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A high-fat diet rich in corn oil reduces spontaneous locomotor activity and induces insulin resistance in mice

Chi Kin Wong[b,1], Amy Botta[a,1], Jason Pither[a], Chuanbin Dai[a], William T. Gibson[b], Sanjoy Ghosh[a,*]

[a]Department of Biology, IKBSAS, University of British Columbia-Okanagan, Canada
[b]Department of Medical Genetics, University of British Columbia, University of British Columbia, Vancouver, Canada

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Abstract

Over the last few decades, polyunsaturated fatty acid (PUFA), especially n-6 PUFA, and monounsaturated fatty acid content in 'Western diets' has increased manyfold. Such a dietary shift also parallels rising sedentary behavior and diabetes in the Western world. We queried if a shift in dietary fats could be linked to physical inactivity and insulin insensitivity in mice. Eight-week old female C57/Bl6 mice were fed either high-fat (HF) diets [40% energy corn oil (CO) or isocaloric olive oil (OO) diets] or chow (n=10/group) for 6 weeks, followed by estimation of spontaneous locomotor activity, body composition and *in vivo* metabolic outcomes. Although lean mass and resting energy expenditure stayed similar in both OO- and CO-fed mice, only CO-fed mice demonstrated reduced spontaneous locomotor activity. Such depressed activity in CO-fed mice was accompanied by a lower respiratory ratio, hyperinsulinemia and impaired glucose disposal following intraperitoneal glucose tolerance and insulin tolerance tests compared to OO-fed mice. Unlike the liver, where both HF diets increased expression of fat oxidation genes like PPARs, the skeletal muscle of CO-fed mice failed to up-regulate such genes, thereby supporting the metabolic insufficiencies observed in these mice. In summary, this study demonstrates a specific contribution of n-6 PUFA-rich oils like CO to the loss of spontaneous physical activity and insulin sensitivity in mice. If these data hold true for humans, this study could provide a novel link between recent increases in dietary n-6 PUFA to sedentary behavior and the development of insulin resistance in the Western world.

Keyword: n-6 PUFA; MUFA; Corn oil; Polyunsaturated fatty acids; Insulin resistance; Diabetes; Locomotor activity; Exercise

1. Introduction

Can the quality of our diets affect our physical activity levels? The relationship between activity, metabolism and diet composition has been simply believed to be a function of total caloric intake or broad macronutrient classes. Studies in foraging animals during cold winters indicate that dietary deprivation of any one or more macronutrients like proteins, fats or carbohydrates affects their behavior and spontaneous activity levels [1]. In omnivores such as rodents, changes in total macronutrient levels of the diets affect spontaneous activity [2]. It still remains unclear if the chemical composition of a macronutrient, independent of caloric intakes, can alter spontaneous activity of any animal. This question becomes crucial if we consider the recent dietary patterns and increasing physical inactivity of another omnivore, humans across the Western world, especially during childhood. Both in the United States and Canada, the number of physically active children has decreased over the last several decades [3,4], which is temporally associated with a radical shift in the chemical composition of dietary fats during this time.

As an omnivore, humans have evolved as hunter-gatherers, having consumed predominantly animal-derived proteins and fats throughout their existence [5]. However, in recent years, to protect against chronic diseases, saturated fatty acids have been extensively substituted with unsaturated fats like monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) in Western food supply. For example, in Canada, increases in dietary fat content over the last century are attributable almost entirely to increases in MUFA and PUFA, whereas saturated fat has remained constant (Table 1) [6]. Although MUFA like palmitoleic acid, as a part of animal tissues, were abundant in traditional human diet [7], the presence of cropseed-based PUFA, especially n-6 PUFA like linoleic acid, was considerably lower and represents a relatively new addition to our dietary niche in abundance [8]. Recent data are unequivocal about the fact that, overall, North American children and youth spend between 40% and 60% of their waking hours in sedentary activities like TV watching, video games etc. [4,9]. In parallel, children in the United States and Canada consume an average of 10.16 g/day and 7.7 g/day n-6 PUFA currently [10,11]. Whether trends in physical inactivity are biologically related to current high trends of unsaturated fats is plausible but remains unknown.

The relationship between macronutrients and physical activity in humans is confounded by multiple confounders like the extent of

* Corresponding author. Department of Biology, IK Barber School of Arts and Sciences, University of British Columbia-Okanagan, ASC 369, 3333 University Way, Kelowna, BC, Canada V1V 1V7. Tel.: +1 250 807 8162; fax: +1 250 807 8001.
E-mail address: sanjoy.ghosh@ubc.ca (S. Ghosh).
[1] denotes equal contribution.

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Table 1
Trends in daily dietary fatty acid intakes in Canada between 1976 and 2005.

	1976	1986	1996	2005	% Increase
Total fats (g))	86.49	88.31	97.98	102.49	18%
Total PUFA (g)	12.56	14.08	17.78	19.61	54%
Total saturates (g)	28.07	27.37	26.60	27.48	0%
Total MUFA (g)	39.61	40.70	47.31	48.75	22%

Data from Statistics Canada — Catalogue No. 21.

surrounding urbanization [12] or socioeconomic factors like income [13], which may override the desire to remain physically active. Such relationships may also be confounded by climate-related variables like sunlight hours and ambient temperature. Moreover, any result obtained from any one country or region may be too narrow in scope to elucidate such relationships. As an example, in North America, where the addition of n-6 PUFA in the food supply is widespread (currently around 7.0±%7.3% energy [14]), the lack of a control population consuming reduced PUFA precludes the use of epidemiological data to estimate a specific effect of PUFA on physical activity at the population level. As an alternative, experimental animal studies could allow us to test the direct biological effect of dietary fat composition on physical activity.

We show that a corn oil diet rich in n-6 PUFA results in loss of spontaneous activity with negative effects on whole-body metabolism, and metabolic gene expressions, leading to insulin resistance in young female mice. If these results hold true for humans, particular attention must be paid to dietary n-6 PUFA as a potential confounder when planning lifestyle interventions for the treatment/prevention of obesity and diabetes.

Table 2
Detailed composition of experimental diets.

Ingredients (g/kg)	Olive oil diet	Corn oil diet
Casein	240	240
DL-Methionine	3.6	3.6
Corn starch	150	150
Sucrose	298.8	298.8
Cellulose	50	50
Calcium carbonate	3.6	3.6
Mineral Mix[a]	42	42
Vitamin Mix[b]	12	12
	Oils	
Soybean oil	10	10
Corn oil	0	190
Olive oil	190	0
Total	1000	1000
Macronutrients	% w/w	% Energy
High-fat diets		
Protein	21.2	19
Carbohydrate	44.4	39
Fat	20.0	40
Total		4.53 kcal/g diet
Normal chow		
Protein	22.6	26.4
Carbohydrate	51.2	60.1
Fat	5.2	13.7
Total		3.41 kcal/g diet

Note: Normal chow ingredients are variable as with any semipurified diet and have not been listed below.
[a]Mineral mix (mg/g): dicalcium phosphate 500, magnesium oxide 24; potassium citrate 220, potassium sulfate 52; sodium chloride 74, chromium KSO_4 $12H_20$ 0.55; cupric carbonate 0.3, potassium iodate 0.01; ferric citrate 6, manganous carbonate 3.5, sodium selenite 0.01, zinc carbonate 1.6; sucrose 118.03.
[b]Vitamin mix (mg/g): vitamin A 0.8; vitamin D_3 1; vitamin E 10; menadione sodium bisulfite 0.08; nicotinic acid 3; calcium pantothenate 1.6; pyridoxine HCl 0.7; riboflavin 0.6; thiamin 0.6; sucrose 978.42.

Table 3
Detailed fatty acid analysis of high-fat diets.

Fatty acid	g/100 g of diet	g/100 g of diet
Σ SFA	2.47	2.81
Σ MUFA	4.9	12.7
Σ PUFA	9.05	1.71
Σ trans FA	0.098	0.04
Total fat	17.4	18.2
Major FA	% in CO diet	% in OO diet
SCFA [C6:0 to C12:0]	<0.1	<0.1
Myristic [C14:0]	0.11	0.17
Palmitic [C16:0]	11.7	11.7
Palmitoleic [C16:1n-7]	0.11	0.73
Stearic [C18:0]	2.01	3.69
Oleic [C18:1n-9]	28.3	70.4
Linoleic [C18:2n-6]	58.3	8.16
Alpha linolenic [C18:3n-3]	1.24	0.98
Behenic [C22:0]	0.14	0.19
Lignoceric [C24:0]	0.16	<0.1
Arachidonic [C20:4n-6]	<0.1	0.61
Eicosapentaenoic [C20:5n-3]	<0.1	<0.1
Docosapentaenoic [C22:5n-6]	<0.1	<0.1
Docosahexaenoic [C22:6n-3]	<0.1	<0.1

CO, corn oil diet; OO, olive oil diet.

2. Experimental methods

2.1. Experimental animals and diet

All animal protocols were approved by the UBC's Animal Care Committee. Eight-week-old female C57/Bl6 mice were fed a high-fat (HF, 40% energy from fat, $n=10$ per HF group) or a "normal" chow (14% energy from fat, $n=10$, Lab Diet-5P76) diet for 6 weeks. The high-fat diets were isoenergetic and isonitrogenous and were prepared commercially (Harlan Teklad, Table 2). The oils used were either 19% w/w corn oil (high-n-6 group, TD.120022) or 19% w/w olive oil (high-MUFA group, TD.130128), both supplemented with 1% w/w soybean oil to avoid essential fatty acid deficiencies. Carbohydrate and protein contents for both HF diets were 44.7% and 21.2% w/w, respectively [15].

2.2. Fatty acid analysis of diets

Fatty acid composition of the diets were analyzed using gas chromatography (GC) by NP Analytical Laboratories (St. Louis, MO, USA) on behalf of Harlan Teklad. In brief, mice food pellets were

Table 4
Primer sequences used for quantification of mRNA levels by real-time PCR in liver and muscle.

Gene	Primer sequences (5'-3')	GenBank Reference #
Peroxisome proliferator activated receptor alpha (*Ppara*)	F: AGCCTCAGCCAAGTTGAAGT R: AGAGGACAGATGGGGCTCTC	NM_001113418.1
Peroxisome proliferator activated receptor delta (*Ppard*)	F: ACCTGGGGATTAATGGGAAA R: CCGTGGGTTTGTCTTCATCT	NM_011145.3
Peroxisome proliferator activated receptor gamma (*Pparg*)	F: TGGGTGAAACTCTGGGAGATTC R: GAGAGGTCCACAGAGCTGATTCC	NM_011146.3
Sterol regulatory element binding transcription factor 1 (*Srebf1*)	F: CTGGAGACATCGCAAACAAGC R: ATGGTAGACAACAGCCGCATC	NM_011480.3
Peroxisome proliferative activated receptor gamma coactivator 1 alpha (*Pgc1a*)	F: TTGCCCAGATCTTCCTGAAC R: TCTGTGAGAACCGCTAGCAA	NM_008904.2
18s ribosomal RNA (*18S rRNA*)	F: CGGCTACCACATCCAAGGAA R: GCTGGAATTACCGCGGCT	NR_003278

Primers used to determine gene expression, both the forward primer (F) and reverse (R) primers are indicated.